TOXICOLOGY

Can a Father's Exposure Lead To Illness in his Children?

In 1990, British epidemiologist Martin Gardner touched off a controversy when he reported that male workers at the Sellafield nuclear fuel processing plant in England were more likely than their neighbors to have children with leukemia. That study not only rang alarm bells for occupational health experts, it flew in the face of previous research indicating that a father's exposure to radiation did not increase his children's chances of cancer. But there's the rub: The previous research was scanty. Indeed, the science of understanding how a father's exposure to toxins is linked to disease and birth defects in his offspring is, well, embryonic, as a recent conference* on "male-mediated toxicity," held in Pittsburgh, made clear.

Like many emerging fields, this one is filled with uncertainties. Big news at the meeting, for example, was early word of a Canadian study that flatly contradicts the Sellafield results. But just as important as the contradictions and uncertainties is the fact that researchers at the conference were getting together and crossing disciplinary lines to find ways of advancing their field. "Unless we're forced to go listen to someone outside our discipline we tend not to," epidemiologist Jennifer M. Ratcliffe of the National Institute of Environmental Health Sciences said at a workshop devoted to figuring out how to forge those key multidisciplinary ties. And forced they were, as geneticists, epidemiologists, and toxicologists immersed themselves in hallway discussions, workshops, and plenary sessions. After 3 days, the consensus was that there is an urgent need for studies to elucidate mechanisms underlying tantalizing evidence that many different types of paternal exposure induce changes in sperm or semen that could affect children's health.

Nothing exemplifies the volatile field better than the flap over the Sellafield data. For years epidemiologists assumed there was no relation between a father's exposure to radiation and childhood leukemia, basing their analysis partly on studies of children of Japanese men exposed to atomic blasts at Hiroshima and Nagasaki. No wonder, then, that Gardner, who works for the British Medical Research Council, set the field abuzz with his suggestion that radiation might have induced cancer-causing mutations in the sperm cells of Sellafield workers (*Science*, 6 April 1990, p.24).

*Male-Mediated Developmental Toxicity, Fathers' Exposures and Their Children's Health, 16 to 19 September, Pittsburgh.

But the Canadian study comes out strongly for a "no-effects" verdict. Sponsored by the Ottawa, Ontario-based Atomic Energy Control Board, a team headed by John McLaughlin, senior epidemiologist at the Ontario Cancer Treatment and Research Foundation, analyzed 112 cases of leukemia in children in the vicinity of four Canadian nuclear facilities between 1950 to 1988 and found no association between childhood leukemia and the occupational exposure of fathers to ionizing radiation before conception. The control board published the study, which was reviewed by a panel that included noted British epidemiologist Sir Richard Doll, last month. "It's a well-done study, they've taken into account just about every conceivable bias, says Robert W. Miller, head of the clinical epidemiology branch at the National Cancer Institute. Says McLaughlin: "When I first launched this work, I thought maybe Gardner really had discovered something. Now the only thing I'm really surprised at is how convincingly null our results were." Gardner is ill and could not be reached for comment. Andrew Hall, a coauthor on the Sellafield study who is an epidemiologist at the London School of Hygiene and Tropical Medicine, said he had not yet seen the Canadian results. But Hall said he stands by the Sellafield research and added that two British groups are currently following up on it with larger studies.

Although McLaughlin's study may persuade many researchers that a father's radiation exposure is not, in fact, linked to leukemia in his children, the Sellafield study has begun to focus attention on accumulating evidence for other forms of male-mediated toxicity. A basic finding, often reproduced, is that men in certain occupations—including painters, mechanics, and farmers—seem to run a significantly higher risk of producing children with birth defects than men in other occupations; the common thread appears to be exposure to chemicals such as solvents or pesticides. "Most studies that look for occupational risk factors [in birth defects] find some," says Jonathan Buckley, an epidemiologist at the University of Southern California.

But these studies are weighed down with caveats, because although it's easy to compare occupational exposures, it's not so easy to ensure that the men aren't exposed to toxins elsewhere in their lives. "You have to remember, these studies arbitrarily focus on occupational as opposed to other avenues of exposure," warns epidemiologist David A. Savitz of the University of North Carolina.

Epidemiology, of course, is only half of the equation that describes male-mediated toxicity. The other half is the biological examination of mechanisms whereby damage to sperm might affect the next generation. In this area, geneticists and toxicologists have had a firm starting point: It's been known for decades that certain toxins and radiation can damage sperm. They've also developed a broad knowledge about how mutations in the DNA of mouse sperm are passed to the fertilized egg and induce developmental abnormalities in offspring. And they're homing in on precisely where potential mutagens act. Research presented at the conference by geneticist Liane Russell of Oak Ridge National Laboratory, a pioneer in radiation-induced mutations in mice, suggests that different chemicals exert their maximum damage on sperm at three stages of sperm production, with most chemicals tested affecting the stage during which early spermatozoa and late spermatids are formed.

ONTARIO HYDRO

Men at work. Nuclear industry workers have no elevated risk of having children with leukemia, according to a new study.

The problem, however, is that none of these defects has been linked specifically to certain types of birth defects or diseases. Many researchers at Pittsburgh agreed that what's needed to move the field forward is a way of using animal models to link epidemiological patterns with biological studies. At the conference, geneticist Andrew Wyrobek of Lawrence Livermore National Laboratory predicted the link will be found in the form of "biomarkers," which can be either precise physical changes in sperm or semen or measurable quantities of a substance in the body that can be tied persuasively to specific diseases. And, in the absence of such advances in understanding, it seems likely that the future of research on male-mediated toxicity holds many more controversies like the one surrounding Sellafield.

–Richard Stone